HYDROGELS BASED ON POLYMERIZED IONIC LIQUIDS AS INNOVATIVE DRUG CARRIERS IN CONTROLLABLE AND INDIVIDUALIZED DOSAGE FORMS

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ABSTRACT

Novel Polymerized Ionic Liquids (PILs)-based Hydrogels as Innovative Drug Delivery Systems are presented. The embedding of drugs in hydrogels enables the "smart" delivery of bioactive molecules from drugs for an oral route of administration. Therefore, a high mechanical strength as well as a favorable pH-dependent swelling behavior is required which is shown in this study. A mechanical compression of PILs-based hydrogels up to 98.5% and a high swelling behavior of poly(VEImBr) hydrogels in a solution with a high pH value is achieved. A significant lower swelling is achieved in a solution with a lower pH value.

Keywords: Hydrogel, Polymerized Ionic Liquids, Drug Delivery

INTRODUCTION

Due to the growing demand for a controlled release of drugs in the pharmaceutical industry, there has been a considerable interest in the development of novel and reliable drug-delivery systems. Therefore, the literature considers various approaches, including the embedding of drugs in hydrogels. Such innovative systems enable the "smart" delivery of bioactive molecules from drugs. However, there are several disadvantages of already existing intelligent hydrogels, such as their low mechanical stability, limited and not completely reversible swelling capacity, and slow response to external stimuli. Due to the inadequate properties of these existing hydrogels our focus is on novel polymerized ionic liquids-based hydrogels as drug carriers for oral route of administration. The aim of this research is to achieve a selective drug release from hydrogels over a defined time period and at a specific location in order to control the duration of the action while minimizing undesired effects outside the site of action.

RESEARCH CONCEPT

In order to investigate the PILs-based hydrogels as innovative drug delivery systems, the dimensionally-stable PILs are being obtained by radical polymerization. An imidazolium-based ionic liquid bearing a vinyl group is polymerized with the cross-linker *N,N'*-methylenebisacrylamide. The embedding of a drug can be achieved by adding an active pharmaceutical ingredient (API) dissolved in water during the synthesis, as shown in Figure 2. As model substances simplified structures of protein kinase inhibitors are used. There are several variation possibilities during the synthesis, which have decisive effect on the synthesis of the hydrogel, e.g. content and type of cross-linker, water content and the ionic liquid. At the same time, however, the properties of the hydrogel is obviously also influenced by the variation.

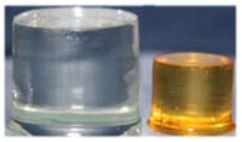

Figure 1. Synthesized Hydrogels in a fresh (left) and dried (right) state.

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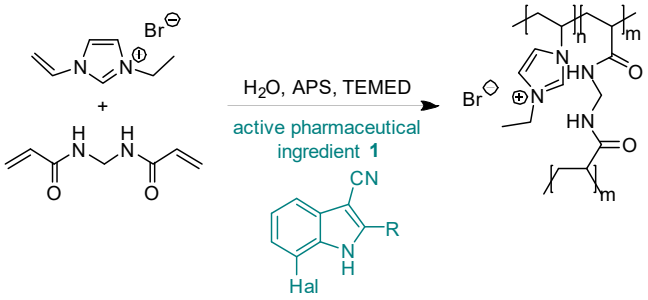

*Figure 2: Synthesis of PILs-based hydrogel poly(VEImBr); radical polymerization of [VEIm] [Br] – 1-Vinyl-3-ethylimidazolium bromide and cross-linker N,N'-methylenebisacrylamide. APS – Ammonium peroxydisulfate, TEMED – N,N,N',N'-tetramethylethane-1,2-diamine, **1** – 7-Halogenindol-3-carbonitrile.*

CHARACTERIZATION

Mechanical Properties

Due to their high water content hydrogels possess generally a weak mechanical strength. However, the advantage of PILs-based hydrogels over e.g. alginate-based hydrogels is their significantly higher mechanical stability [Bandomir, 2014]. The mechanical properties are affected by the IL monomer, composition, cross-linking density, degree of drying or swelling and drying method. A reversible compressibility (ε) of a fresh synthesized poly(VEImBr) hydrogel in physiological saline of up to 72% without crack formation is achieved. This compression behavior is increased by increasing the drying time in a climatic chamber.

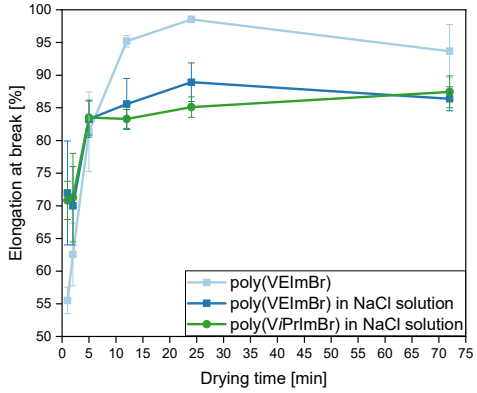

Figure 3: Elongation tests of poly(VEImBr) and poly(ViPrImBr) hydrogels with different degrees of drying at 25 °C and 60% RH partially in 0.9% NaCl solution with a loading speed of 0.1%/s.

With increased drying time, the reversible compression without crack formation increased already up to 98.5% in the air and up to 88.9% in physiological saline for poly(VEImBr), for poly(V*i*PrImBr) up to 87.4%, as shown in Figure 3.

Swelling behavior

The swelling property of hydrogels is a significant factor for controlled drug releases [Rizwan, 2017]. Drug release generally involves the simultaneous absorption of water and desorption of a drug via a swelling-controlled diffusion mechanism. The produced hydrogels show a pH-dependent swelling behavior, as shown in Figure 4**Fehler! Verweisquelle konnte nicht gefunden werden.**. Due to the large variations of pH-values at various body sites, the swelling and thus the release of the API will only take place at the desired site of action in the body. By further functionalization of the PILs, the swelling behavior of the hydrogels as well as the drug release can be affected crucial.

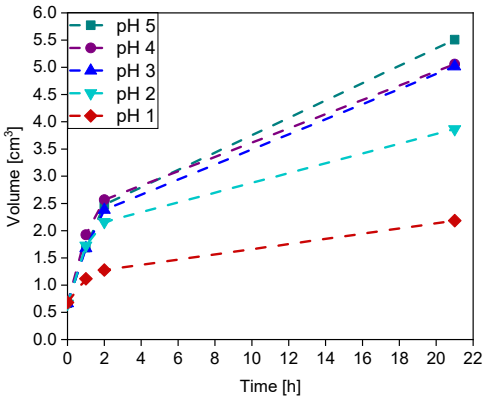

Figure 4: Swelling trend of fresh poly(VEImBr) hydrogels in 0.9% NaCl solution with different pH-values.

Drug release behavior

Initial findings on the drug release behavior can be adapted from catalyst-leaching experiments [Großeheilmann, 2015]. Leaching behavior with different drying methods, catalyst structures, water content, and solvents was investigated. Due to these experiments, drug release mechanisms can be influenced by various parameters, such as drying methods, crosslinker-to-IL ratio, IL monomer, solvent / pH of the aqueous medium, drug size, and drug polarity. The first studies on drug release behavior of model substances are currently under investigation. As model substances simplified structures of protein kinase inhibitors, which are used in the development of drugs for Down syndrome and Alzheimer's disease, are used.

Biocompatibility

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Initial experiments show that most of the IL monomers are toxic before polymerization, except monomers with an isopropyl group. Fortunately, the PILs-based hydrogels show low to no toxicity after polymerization. Further biocompatibility tests are currently under investigation. In addition, the change from a batch process to a continuous process for washing out unreacted IL monomer from the PILs is currently being developed to obtain biocompatible PILs-based hydrogels.

CONCLUSIONS

Stable PILs-based hydrogels were successfully synthesized by a radical polymerization. The mechanical stability of these hydrogels is shown by a reversible compression up to 90% without crack formation. Initial findings show low to no toxicity after polymerization. Drug release can be controlled by pH-dependent swelling behavior. In future, an increased pH-responsive drug release should be obtained by functionalizing the PILs.

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NOMENCLATURE

API	Active Pharmaceutical Ingredient
APS	Ammonium peroxydisulfate
IL	Ionic Liquid
PILs	Polymerized Ionic Liquids
RH	Relative Humidity
TEMED	*N,N,N',N'*-Tetramethylethane-1,2-diamine
VEImBr	1-Vinyl-3-ethylimidazolium bromide
V*i*PrImBr	1-Vinyl-3-isopropylimidazolium bromide
ε	Compressibility

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